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(54) Apparatus for analyzing particles.

(57) A sample liquid flow (18) contains particle components such as blood and urine and is illuminated with fluorescence excitation light from a light source (10). Spectral means (28) such as a prism or a diffraction grating is used to produce a spectrum of the fluorescence emitted by the particles. The fluorescence spectrum is amplified by an image intensifier (30). Then, the intensity of different wavelengths of the fluorescence spectrum is measured by an image sensor (34). The image sensor (34) is reset for each particle.

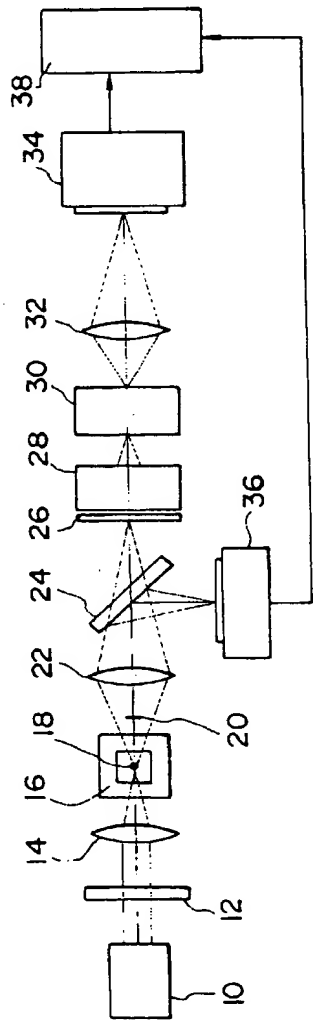

FIG.1

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The present invention relates to apparatus for analyzing a sample liquid containing particles such as blood and urine, by irradiating the sample liquid with light, detecting signals from the particles, and analyzing the particles. The apparatus obtains spectra of light signals by using spectral means such as a prism or diffraction grating, so as to obtain more specific particle information.

In the prior art, a fluorescent excitation (excited) light is irradiated at a sample liquid containing particles such as dyed cells, and the fluorescence emitted from the particles is detected, and the particles are classified and counted. An example of such apparatus is a flow cytometer. Also known is an imaging flow cytometer for picking up the particle images.

In such apparatus, when measuring the fluorescence emitted from the cells, in order to separate the desired fluorescence from other light, wavelength selection means such as an optical filter and a dichroic mirror is needed. Besides, when measuring a plurality of fluorescences of different wavelengths, a corresponding plurality of optical detectors are needed.

Japanese Laid-open Patent Hei. 2-24535 discloses a flow cytometer capable of calculating the fluorescence intensity distribution (intensity against wavelength) of the particles, by separating the fluorescence from the specimen into consecutive wavelength components by spectroscopic means, and detecting the separated wavelength components by using a one-dimensional photoelectric detector.

With the optical filter, however, it is difficult to separate beams of light of similar wavelengths, although it is possible to separate beams of light of very different wavelengths. In addition, the wavelength distribution of the light cannot be measured. That is, it is not possible to know the quantity of fluorescence of a particular wavelength that is emitted from a particular position of a cell. This may be possible by taking the cell image by using a video camera and analyzing the image, but each cell must be imaged and the image processed. Thus, the apparatus becomes complicated.

In the apparatus for analyzing particles disclosed in the Japanese Laid-open Patent Hei. 2-24535, moreover, since the separated fluorescence is weak, it is difficult to detect the fluorescence directly with the detector. By increasing the lighting (irradiation) intensity of the fluorescence excitation light, the fluorescence intensity may be enhanced, but the particles to be analyzed may become damaged.

Besides, when using a photoelectric conversion element of charge accumulation type such as a charge coupled device (CCD), unless the accumulated charge is reset by some way or other, the fluorescence of all particles passing through the detection region is added up (integrated). Since the particle interval is not constant, it is necessary to detect the passing of a particle, and reset the charge on every occasion.

According to the present invention, there is provided apparatus for analyzing particles, comprising: a first light source for illuminating with fluorescence excitation light a sample liquid flow containing particles; spectral means for separating fluorescence emitted in a specific direction from a particle to produce a fluorescence spectrum; amplifying means for amplifying the fluorescence spectrum produced by the spectral means; an image sensor for detecting different wavelengths of the amplified fluorescence spectrum; and signal processing means for receiving a signal from the image sensor and resetting the signal of the image sensor for each particle.

With the invention, it is possible to analyze a particle by measuring the fluorescence spectrum with high precision even if the fluorescence emitted by the particle is of low intensity.

Preferably, the sample liquid is formed into a sheath flow in which the suspension of particles is covered with a laminar sheath liquid in order to align the particles in a row near the middle of the liquid flow. Usually the sheath liquid is a diluent liquid or the like.

The fluorescence emitted from the particle as a result of irradiation with the fluorescence excitation light is separated by the spectral means, and a fluorescence spectrum is obtained. This fluorescence spectrum is amplified by the amplifying means, such as an image intensifier, and the intensity of a range of wavelengths may be measured by the image sensor.

If the image sensor comprises a plurality of rows or lines of one-dimensional images sensors, the fluorescence spectra of a plurality of particles can be measured simultaneously.

If the fluorescence excitation light passing through the particle and the scattered light scattered by the particle are detected by a light detecting means, passage of the particle through a detection region may be judged by the signal processing means. In response to the passing of the particle, the signal of the image sensor is reset, before the signal is read out (if the particle is not of interest) or after the signal is read out (if the particle is of interest).

Non-limiting embodiments of the invention will now be described with reference to the accompanying drawings, in which:-

Fig. 1 is a schematic diagram showing an embodiment of an apparatus for analyzing particles in accordance with the invention;

Fig. 2 is a characteristic diagram of dichroic mirror of Fig. 1;

Fig. 3 is a perspective explanatory diagram showing the detail around the spectroscopic means of Fig. 1;

Fig. 4 is a schematic diagram showing another embodiment of the invention;

Fig. 5 is a schematic diagram showing another embodiment of the invention;
Fig. 6 is a schematic diagram showing a different embodiment of the invention;
Fig. 7 is an explanatory diagram showing an irradiation region of an excitation light source and an image pickup region of a CCD camera in a flow cell unit of Fig. 6;
Fig. 8 is a schematic diagram showing another different embodiment of the invention;
Fig. 9 is a schematic diagram showing another embodiment of the invention;
Fig. 10 is a schematic diagram showing another embodiment of the invention;
Fig. 11 is a perspective explanatory diagram showing the spectroscopic means of Fig. 10; and
Fig. 12 is a schematic diagram showing another embodiment of the invention.

Embodiment 1

Fig. 1 is a schematic diagram of an apparatus for analyzing particles in Embodiment 1.

A light source 10 is a fluorescence excitation (excited) light source, which is a laser light source such as Ar,He-Cd or semiconductor laser, or a light source of continuous emission type such as Xe lamp. When a light source with continuous spectrum such as Xe lamp is used, a desired excitation (excited) wavelength can be selected by using a wavelength selection filter 12. When the laser light source is used, the filter 12 is unnecessary.

A condensing lens 14 is a lens for focusing the light from the fluorescence excitation light source 10 into a sample liquid flow 18 flowing in the center of a flow cell 16, and the spot size when concentrated is desired to be about 10 x 200 μm.

The flow cell 16 is made of transparent material of glass or plastics, and comprises a lead-in passage narrowed gradually, a narrow measuring passage connected to the lead-in passage, a sheath liquid feeding port provided in the lead-in passage, and a discharge port provided downstream of the measuring passage.

When the particle to be analyzed passes through the illumination region of the fluorescence excitation light, scattered light (forward scattered light) and fluorescence (forward fluorescence) are obtained. Both types of light are collected by a receiving lens 22. Numeral 20 is a shield plate for shielding the direct light from the light source 10.

The scattered light is reflected by a dichroic mirror 24, and enters light detecting means, such as a CCD line sensor 36. The signal from the line sensor 36 is fed into the signal processor 38, and passing of the particle is detected. At the same time, the size and number of passing particles are detected. When sensing the particle by the transmitted light, the shield plate must be removed.

On the other hand, the fluorescence passes through the dichroic mirror 24 and through a slit 26 and enters the spectroscopic means 28. Fig. 2 shows the characteristic diagram of the dichroic mirror 24.

The spectroscopic means 28 is for converting the fluorescence emitted from the cell into a spectrum. For example, by using polychromator, prism or lattice (grating), a fluorescence spectral image as shown in Fig. 3 is obtained on the incident plane of amplifying means, such as image intensifier 30. Numeral 58 denotes a particle.

The image intensifier 30 is a photoelectron multiplier, and is used for amplifying the fluorescence spectral image separated by the spectroscopic means 28. The fluorescence spectral image entering the incident plane (photoelectric plane) of the image intensifier 30 is amplified, and sent out to an output plane (fluorescence plane) of the image intensifier 30. Furthermore, the fluorescence spectral image sent out of the image intensifier 30 is focused on a light receiving element (image sensor) 34 by a relay lens 32 or an optical fiber.

By using a CCD line sensor or a photo diode array as the light receiving element (image sensor) 34, the fluorescence intensity of each wavelength is measured. For example, using a CCD line sensor with 256 pixels of 13μm each, and measuring in the wavelength region from 400 to 656 nm, by properly setting the focal length of the spectroscopic means 28, the fluorescence intensity can be measured at a resolution of 1 nm per pixel.

When a CCD line sensor is used as a light receiving element (image sensor) 34, since it is of charge accumulation type, i.e. different to a photo diode array, the accumulated charge must be reset by some way or other (otherwise the fluorescence intensity of all passing particles is counted (added) up). Accordingly, by making use of the signal from the line sensor 36 as the light detector, the accumulated charge is read out after every passing of particle, and the charge is reset. Besides, by processing the signal from the line sensor 36, it is judged whether the particle is to be measured or not and,in the case of a particle not to be measured, the fluorescence spectral signal is reset from the CCD line sensor 34 before reading out to the signal processor 38, so that only necessary data is taken in.

The obtained signal is processed by the signal processor 38, and the spectral data may be obtained for every passing particle.

Because the excitation (excited) light and fluorescence light at the light receiving element 34 differ in wavelength, the position of the pixel for each wavelength signal is different. Hence, filter for removing excitation light is not needed.

Besides, for limiting the detecting region in the flow cell 16, circular or rectangular slit 26 must be in-

stalled. Since the size of the slit 26 is determined by the imaging magnification of the receiving lens 22, the size of the slit 26 may be 0.2 mm in diameter in the case of, for example, the detecting region in the flow cell being 2 μm in diameter and the imaging magnification of the receiving lens 22 being 10 times.

Thus is realized the flow cytometer capable of acquiring fluorescence in two or more types (kinds) of wavelengths by using one detecting system.

Embodiment 2

The apparatus in Fig. 1 is designed to detect the forward scattered light and forward fluorescence caused by fluorescence excitation light from the light source 10, but other embodiments can be also realized.

For example, Fig. 4 is a schematic diagram of an apparatus for analyzing particles in Embodiment 2.

The apparatus in Fig. 4 is different from the apparatus in Fig. 1 in the configuration (arrangement) of the illumination system of the light source 10 (illumination system of fluorescence excitation light) and the scattered light detection system of the light (photo) detecting means 36, and the apparatus in Fig. 4 is intended to detect the forward scattered light and backward fluorescence.

By the arrangement of the irradiation system and the mirror 24, the excitation light from the light source 10 does not enter directly into the fluorescence detecting system, so that fluorescence measurement at high precision is realized.

Embodiment 3

Fig. 5 is a schematic diagram of an apparatus for analyzing particles in Embodiment 3.

The apparatus in Fig. 5 is further different from the apparatus in Fig. 4 in the arrangement of the scattered light detecting system of the light detecting means 36, and the apparatus in Fig. 5 is intended to detect the side scattered light and backward fluorescence. The shielding plate 20 for detecting the side scattered light is not needed.

In this case, too, the same effects as in the apparatus in Fig. 4 may be obtained. In addition, since the side scattered light is detected, a signal reflecting (influencing) the difference in the internal structure of particles may be obtained.

Embodiment 4

Fig. 6 is a schematic diagram of an apparatus for analyzing particles in Embodiment 4.

This embodiment shows an arrangement of an apparatus for picking up white light images of cells emitting fluorescence of a specific wavelength by utilizing the signal obtained in Embodiment 1. As the light source, in addition to the fluorescence excitation light source 10, a pulse emission type light source in the visible light region (for example, Xe flash lamp) is used as a cell image pickup light source 40. The irradiation light from the light source 40 is transformed into parallel light in a collimator lens 42, and enters a half-mirror 46.

The half-mirror 46 is used for matching the irradiation regions of the excitation light source 10 and pickup light source 40, and the ratio of transmitted light and reflected light is determined freely by the quantity of light required in the fluorescence receiving system and cell pickup system, but it is desired to heighten the transmissivity of the light from the excitation light source 10 by setting the transmissivity at 90% and the reflectivity at 10% in order to intensify the fluorescence intensity.

A half-mirror 48 is designed to pass the fluorescence obtained from the cell and reflect the cell pickup light, and the ratio of the reflected light and transmitted light can be determined according to the quantity of light required in each system, same as in the case of the half-mirror 46.

An electronic shutter 50 is used to prevent excessive light from entering the image intensifier 30 when the cell image pickup light source 40 emits light. Instead of this electronic shutter, an image intensifier possessing a gate function may be used.

The image pickup means, for example a CCD camera 52, is intended to pick up the white light image of the cell. However, if the pickup region of the CCD camera and the irradiation region of excitation light are overlapped, the excitation light is always entering the CCD camera, and the CCD element is saturated by the luminance (brightness), and therefore, as shown in Fig. 7, the irradiation region 56 of the excitation light source 10 and the pickup region 57 of the CCD camera 52 must be separate. Numeral 58 denotes a particle. As the excitation light source 10, if the light source such as He-Cd laser for emitting the light in the wavelength outside the visible region or at the end of visible region is used, this light does not affect the color imaging of the cell.

The signal processor 54 processes the signal from the light receiving element (image sensor) 34 and judges if the cell in the process of passing the pickup region is to be measured or not, and if judged to be the target cell a trigger pulse is generated to activate the cell image pickup light source 40, while the obtained signal is analyzed.

The measuring procedure is explained below.

The fluorescence excitation light source 10 always illuminates the particle passing region of the flow cell 16, and monitors passing of cells. When a cell dyed with fluorescent dye passes, the fluorescence emitted from the cell and the remaining excitation light are condensed by the receiving lens 22, and pass through a half-mirror 48, and the excitation light

component is removed by the dichroic mirror 24, and the remaining light passes through a circular slit 26, and enters the spectroscopic means 28. The fluorescence light entering the spectroscopic means 28 is separated into spectra, and passes through the electronic shutter 50, and a spectral image as shown in Fig. 3 is focused on the image intensifier 30. This spectral image is amplified by the image intensifier 30, and is output at the fluorescent plane of the image intensifier 30. The spectral image produced on the fluorescent plane of the image intensifier 30 is focused on the light receiving element 34 by the relay lens 32. At this time, instead of the relay lens 32, the image may be also focused on the light receiving element 34 by using an optical fiber.

A similar effect is obtained when the electronic shutter 50 is disposed behind (downstream of) the spectroscopic means 28. Moreover, without using the electronic shutter 50, the same effect may be obtained by using an image intensifier with gate function.

Afterwards, the detected signal is analyzed by the signal processor 54. When the particle is double-dyed in FITC (fluorscein isothiocyanate) and phycoerythrin, the particle to be measured is dyed in FITC or phycoerythrin or in both, and hence the fluorescence wavelength emitted from the particle is either 530 nm or 570 nm, or both. Accordingly, when either one of the fluorescence intensity at 530 nm and 570 nm is more than a specific value or both are more than specific values, the white light image pickup light source 40 is activated. Furthermore, the pictured particle images are classified and stored according to fluorescence wavelength (in three types, that is, 530 nm, 570 nm, and both). Alternatively, comparing the measured fluorescence wavelength pattern with a preset fluorescence wavelength pattern, if the wavelength patterns are matched, the white light image pickup light source 40 is activated.

To pick up a still cell image, the emission time of the white light image pickup light source 40 must be a sufficiently short time, otherwise the still image is not obtained. This emission time is determined by the velocity of the cell passing through the pickup region. For example, if the cell velocity is 1 m/sec, the emission time must be 1 μsec or less.

At the same time, the electronic shutter 50 is operated, so that strobe light may not enter the image intensifier 30.

The light emitted from the white light image pickup light source 40 passes through the half-mirror 46, and irradiates the cell in the flow cell 16. As a result, the light passing through the cell is focused by the receiving lens 22, and is reflected by the half-mirror 48, and is focused on the CCD camera 52.

In this way, the white light image of the cell emitting fluorescence of a specific wavelength is acquired.

Embodiment 5

In the apparatus shown in Fig. 6, the irradiation system of the fluorescence excitation light of the light source 10, and the irradiation system of pulse light for image pickup of the light source 40 are disposed on the same optical axis, and the detection systems of scattered light, fluorescence, and particle image light are disposed on the same optical axis so as to detect the forward scattered light, forward fluorescence and transmitted light image, but other embodiments may be also executed.

For example, Fig. 8 is a schematic diagram of an apparatus for analyzing particles in Embodiment 5.

The apparatus in Fig. 8 is different from the apparatus in Fig. 6 in the arrangement of the irradiation system of fluorescence excitation light of the light source 10, and is intended to detect the side scattered light of the light source 10, side fluorescence of the light source 10, and transmitted light image of the light source 40. The shield plate 20 for detecting side scattered light is not needed.

Moreover, in the arrangement of the apparatus in Fig. 6, when both the light of the light source 10 and light of light source 40 are visible, a half-mirror or dichroic mirror for reflecting the light from the light source 10 must be used as the mirror 46, and therefore the light from each light source cannot be led efficiently into the flow cell 16. However, in the arrangement of the apparatus in Fig. 8, since mirror 46 is not used, it is advantageous because the light from the light source 10 and the light from the light source 40 can be directly and efficiently irradiated at the flow cell 16.

Embodiment 6

Fig. 9 is a schematic diagram of an apparatus for analyzing particles in Embodiment 6.

The apparatus in Fig. 9 is different from the apparatus in Fig. 6 in the arrangement of the irradiation system of pulse light for particle pickup of the light source 40 and the pickup system of particle transmitted light image, and the apparatus in Fig. 9 is intended to detect the forward scattered light of the light source 10, forward fluorescence of the light source 10, and the transmitted light image of the light source 40.

In this embodiment, compared with the apparatus for analyzing particles in Embodiment 4, the system for picking up white light image is disposed at a position orthogonal to the optical system for detection of fluorescence.

In this arrangement, since it is not necessary to use the half-mirrors 46, 48 of Fig. 6, there is the advantage that the light of the light sources 10, 40 can be utilized efficiently. Numeral 15 is a condenser, 23 is a receiving lens, and 60 is a signal processor.

Embodiment 7

Fig. 10 is a schematic diagram of an apparatus for analyzing particles in Embodiment 7.

The basic arrangement of this embodiment is the same as Embodiment 1. The differences of this embodiment are as follows: 1. the sample liquid flow is a flat flow 64, instead of a circular flow; 2. the light receiving element for detecting the fluorescent spectral image is a two-dimensional image sensor 70, instead of a one-dimensional image sensor; 3. the slit is a rectangular slit 68 broad (wide) in the lateral direction, instead of the circular one.

Fig. 11 is a magnified view of essential parts of Fig. 10. Since the sample liquid flow 64 is a flat flow, the number of particles to be analyzed can be increased. Besides, using a two-dimensional image sensor 70, a spectral distribution diagram for each point in the X-direction may be obtained. Besides, in order to obtain a flat sample liquid flow 64 in the flow cell 16, the lead-in passage of the flow cell 16 is gradually narrowed in width only in one direction of the passage.

For example, supposing the measuring region in the flow cell 16 to be 20 x 150 μm and the imaging magnification of receiving lens 22 to be 40 times, when the slit 68 before (upstream of) the spectroscopic means 28 is 6 x 0.8 mm, the size of one pixel is 40μm in the light receiving element (two-dimensional image sensor) 70, and the CCD area sensor has 150 x 250 pixels (150 pixels in the X-direction, 250 pixels in the Y-direction), the fluorescent spectrum from the cell can be measured in the entire measuring region, and the wavelength resolution of 1 nm per 1 pixel of CCD can be attained.

Herein, by processing the signal obtained from the light receiving element 70 by the signal processor 72, the wavelength of the fluorescence emitted simultaneously from a plurality of cells can be measured.

Besides, when the wavelength of the fluorescence emitted from the cells is limited in a specific wavelength region, for example, when using FITC (fluorescein isothiocyanate), phycoerythrin, and propidium iodine as fluorescent dyes, by placing the line type CCD sensor or photo diode array at the Y-axis position corresponding to the wavelengths of 530 nm, 570 nm, and 610 nm, only the intended spectral component can be measured. Numeral 62 is a condenser and 66 is a shield plate.

Embodiment 8

Fig. 12 is a schematic diagram of an apparatus for analyzing particles in Embodiment 8.

In this embodiment, the system for white light image pickup is added to the apparatus of Embodiment 7 shown in Fig. 10. In this arrangement, the signal obtained from the detector (two-dimensional image sensor) 70 is analyzed by the signal processor 74. When a cell emitting fluorescence coinciding with predetermined conditions is detected (for example, when double-dyed in fluorescein isothiocyanate and phycoeryrhin, and either 530 nm or 570 nm fluorescence intensity is more than a specific value, or when both are more than specific values), the white light image pickup light source 40 is used to form a cell image in the CCD camera 52. Numeral 44 is a wavelength selection filter.

In the embodiments in which the sample liquid flow is a flat flow, it is possible to vary the arrangement of the optical system.

Being thus constructed, the embodiments have the following characteristics.

(1) The fluorescence from the spectroscopic means such as a prism or a diffraction grating is separated by wavelength, and amplified by an image intensifier, and the intensity is measured by an image sensor at each wavelength, and therefore a plurality of fluorescence intensities can be measured simultaneously for individual particles with high precision. Besides, a fluorescent spectral image can be obtained.

(2) The light is separated by spectroscopic means, instead of wavelength selection filter, so that it is possible to separate clearly if the wavelengths are close to each other

(3) When the sample liquid flow is a flat flow, and a two-dimensional image sensor is used as an image sensor, the fluorescent spectra of a plurality of particles can be measured at the same time.

Having described preferred embodiments of the invention with reference to the accompanying drawings, it is to be understood that the invention is not limited to those precise embodiments, and that various changes and modifications may be effected thereto by one skilled in the art without departing from the invention.

Claims

1. Apparatus for analyzing particles, comprising:

a first light source (10) for illuminating with fluorescence excitation light a sample liquid flow (18) containing particles;

spectral means (28) for separating fluorescence emitted in a specific direction from a particle to produce a fluorescence spectrum;

amplifying means (30) for amplifying the fluorescence spectrum produced by the spectral means (28);

an image sensor (34) for detecting different wavelengths of the amplified fluorescence spectrum; and

signal processing means (38) for receiving

a signal from the image sensor (34) and resetting the signal of the image sensor for each particle.

2. Apparatus for analyzing particles according to claim 1, further comprising light detecting means (36) for detecting light scattered by the particle or transmitted light passing through the particle.

3. Apparatus for analyzing particles according to claim 2, wherein the light detecting means (36) is disposed to detect forward scattered light and forward fluorescence.

4. Apparatus for analyzing particles according to claim 2, wherein the light detecting means (36) is disposed to detect forward scattered light and backward fluorescence.

5. Apparatus for analyzing particles according to claim 2, wherein the light detecting means (36) is disposed to detect side scattered light and backward fluorescence.

6. Apparatus for analyzing particles according to any one of claims 1 to 5, further comprising a second light source (40) for emitting a pulse of light at the particle, and image pickup means (52) for picking up an image produced by transmitted pulse light passing through the particle.

7. Apparatus for analyzing particles according to claim 6, wherein the optical path from the sample liquid flow (18) to the spectral means (28) has, at least initially, the same optical axis as the optical path from the sample liquid flow (18) to the image pickup means (52).

8. Apparatus for analyzing particles according to claim 6, wherein the optical path from the sample liquid flow (18) to the spectral means (28) is, at least initially, substantially orthogonal to the optical path from the sample liquid flow (18) to the image pickup means (52).

9. Apparatus for analyzing particles according to claim 6, 7 or 8, wherein the optical path from the first light source (10) to the sample liquid flow (18) is, at least adjacent to the sample liquid flow (18), substantially orthogonal to the optical path from the second light source (40) to the sample liquid flow (18).

10. Apparatus for analyzing particles according to any one of claims 1 to 9, wherein:

the apparatus is arranged to form a sheath flow by enveloping the sample liquid flow (64) with a sheath liquid and to pass the sheath flow through a flow cell (16);

the sample liquid flow (64) is a flat flow wide in one direction and narrow in another direction;

the spectral means (28) is arranged to separate fluorescence emitted from one of the wide sides of the flat sample liquid flow (64); and

the image sensor is a two-dimensional image sensor (70).

11. Apparatus for analyzing particles according to claims 2 and 10, wherein the light detecting means (36) is arranged to detect light scattered by the particle out of one of the wide sides of the flat sample liquid flow (64) or transmitted light passing through the particle.

FIG.1

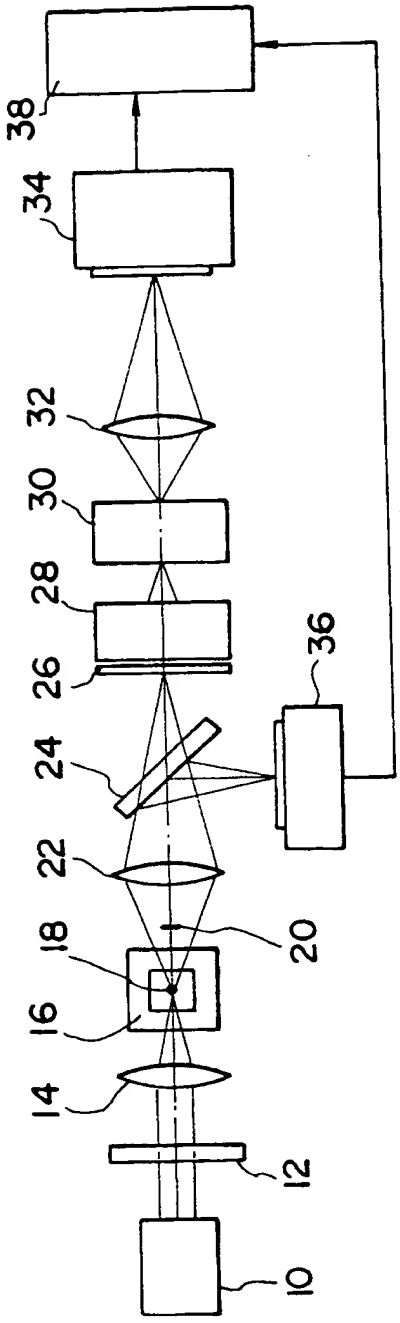


FIG.2

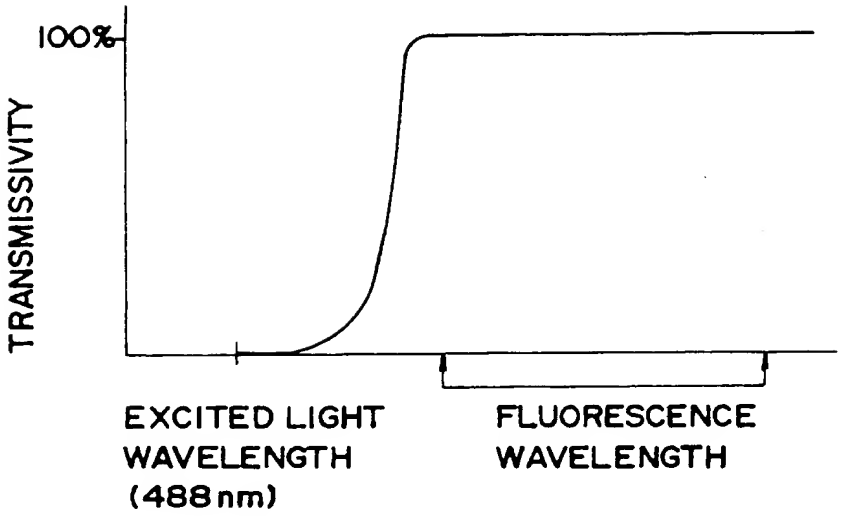


FIG.3

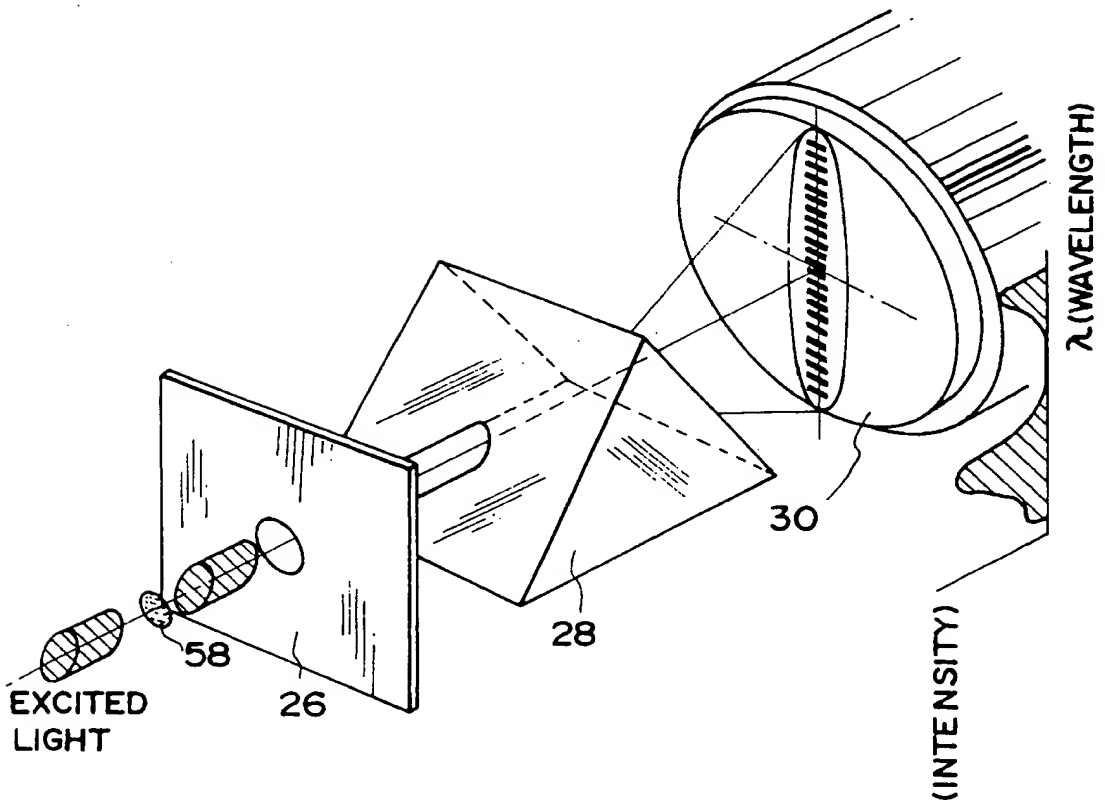


FIG.4

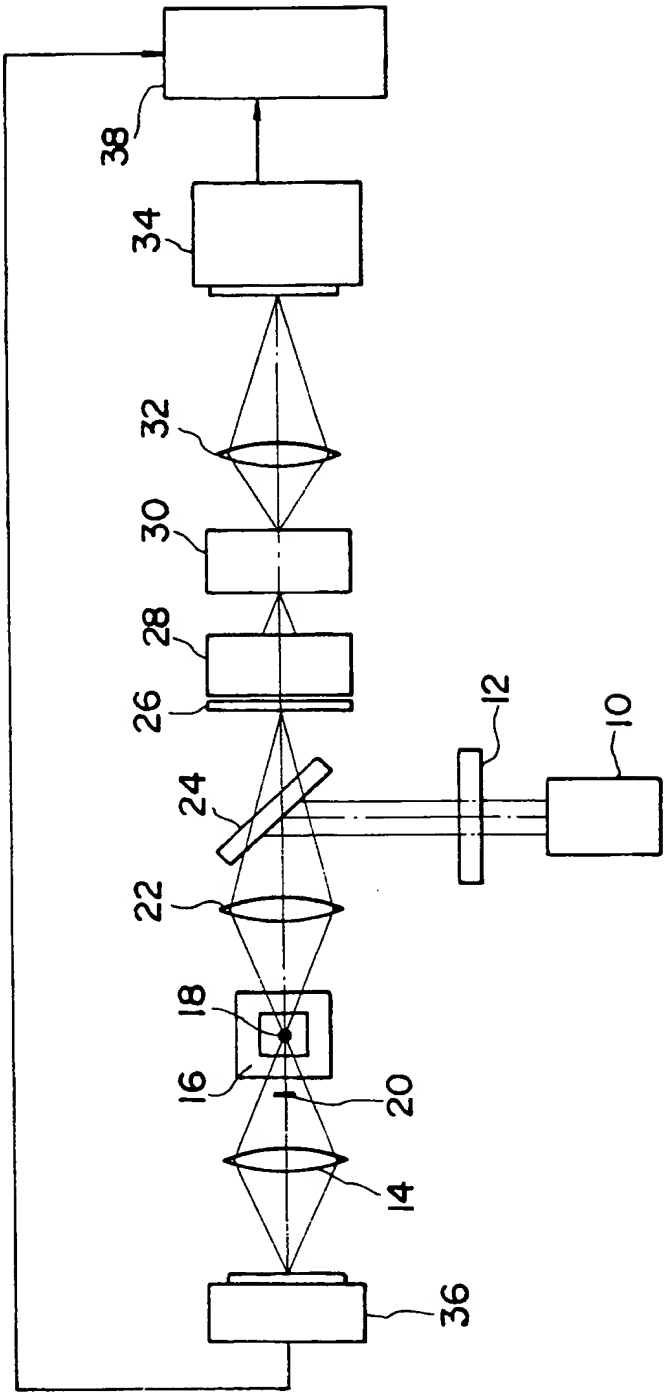


FIG.5

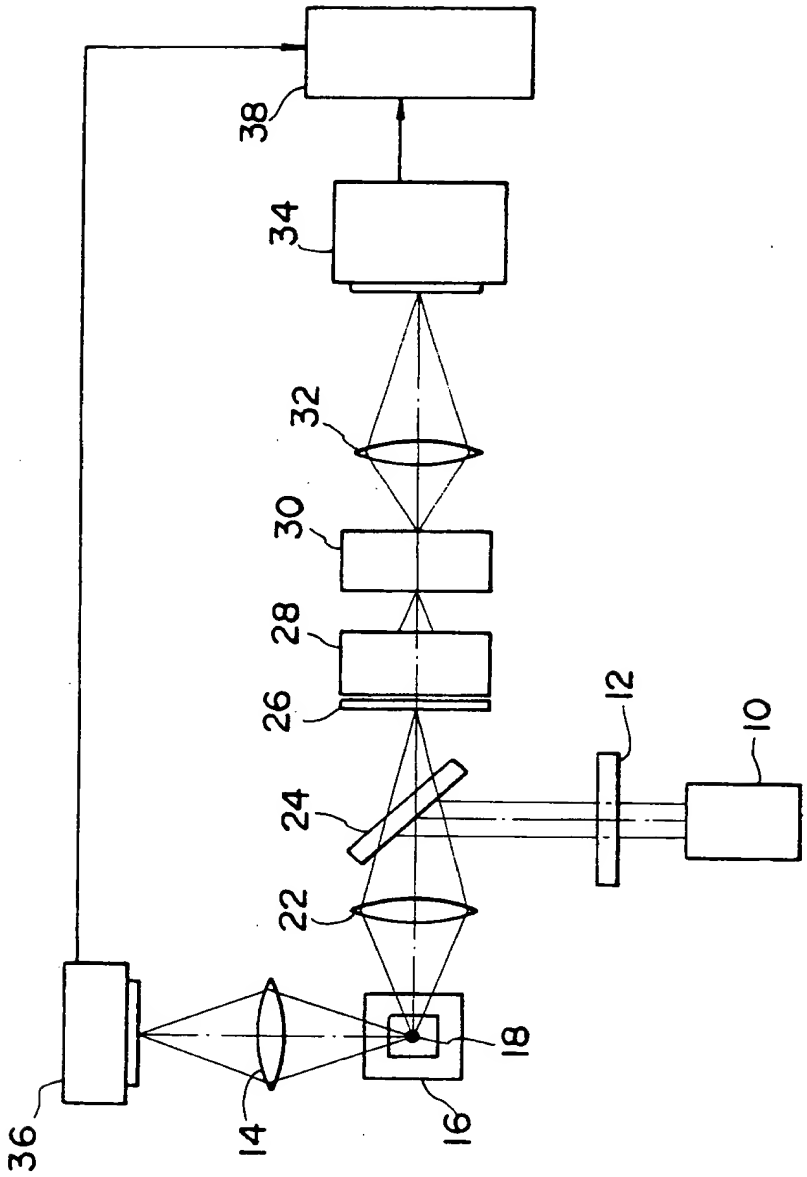


FIG 6

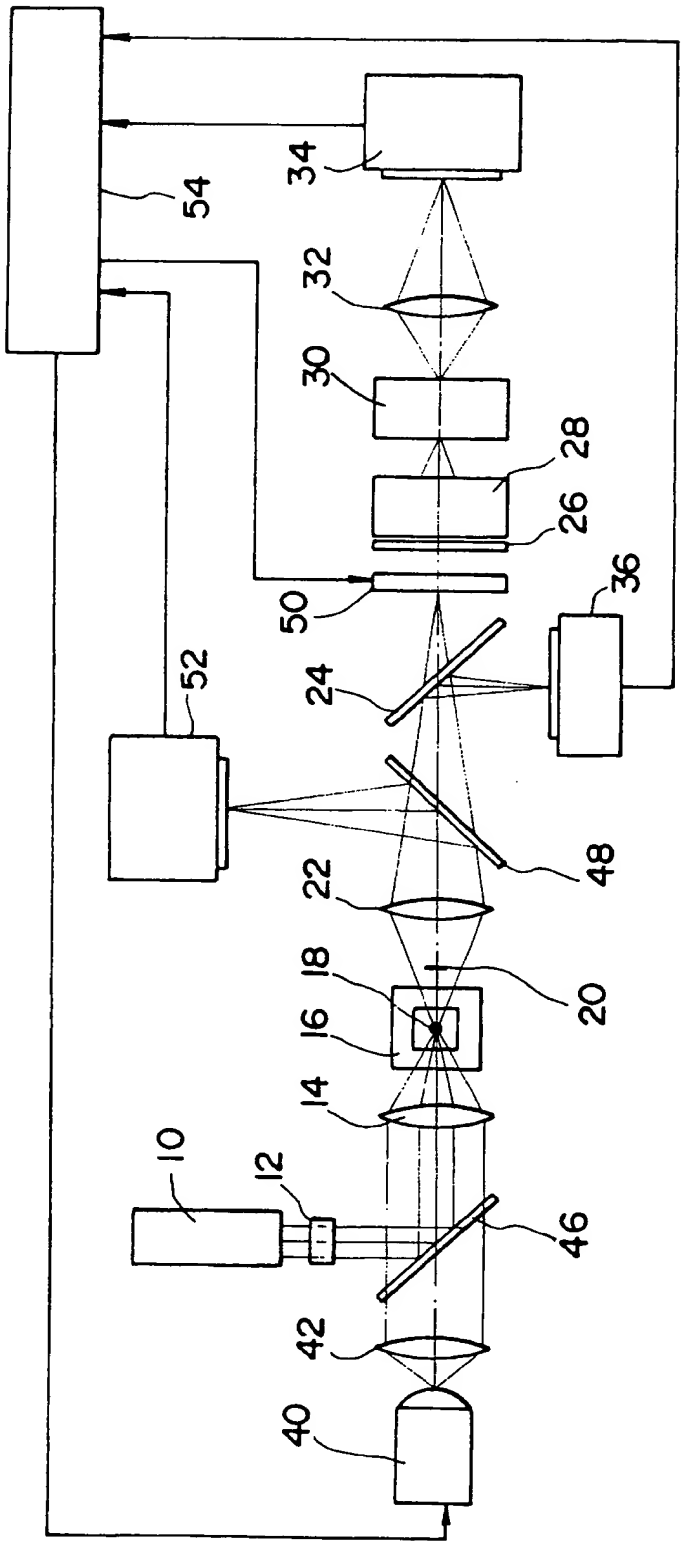


FIG.7

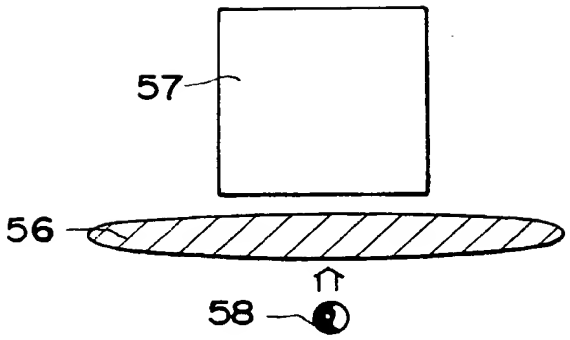


FIG.11

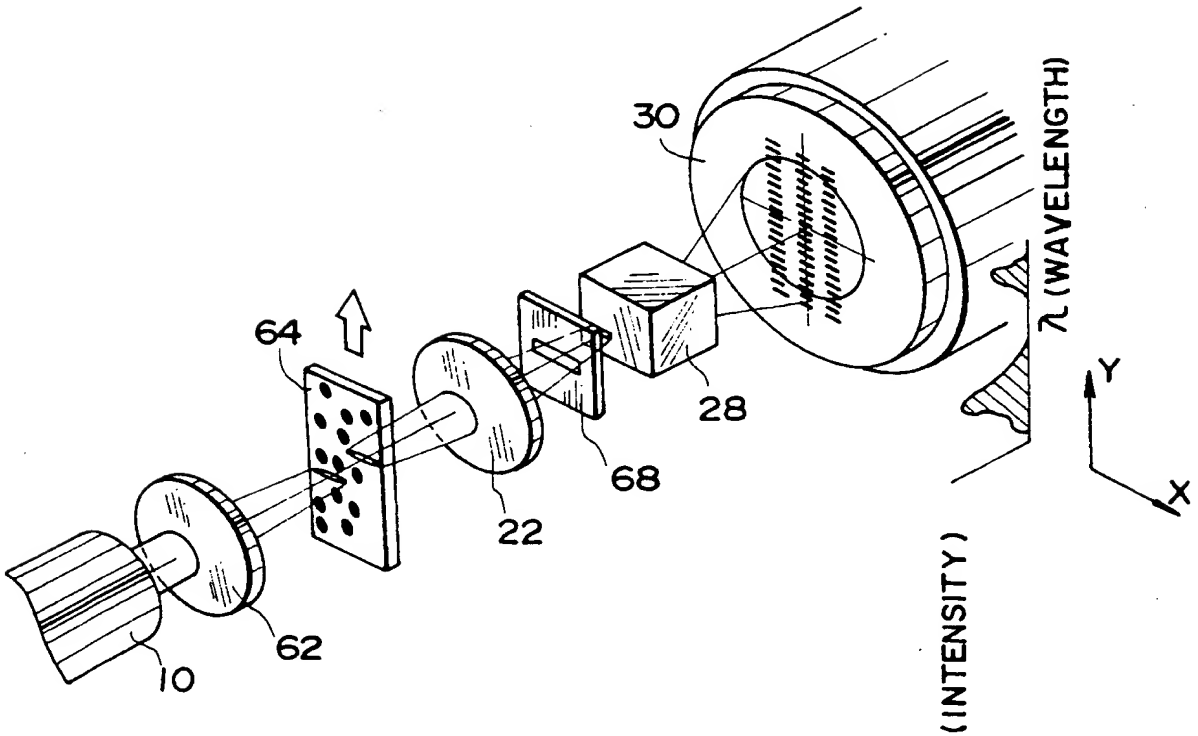


FIG.8

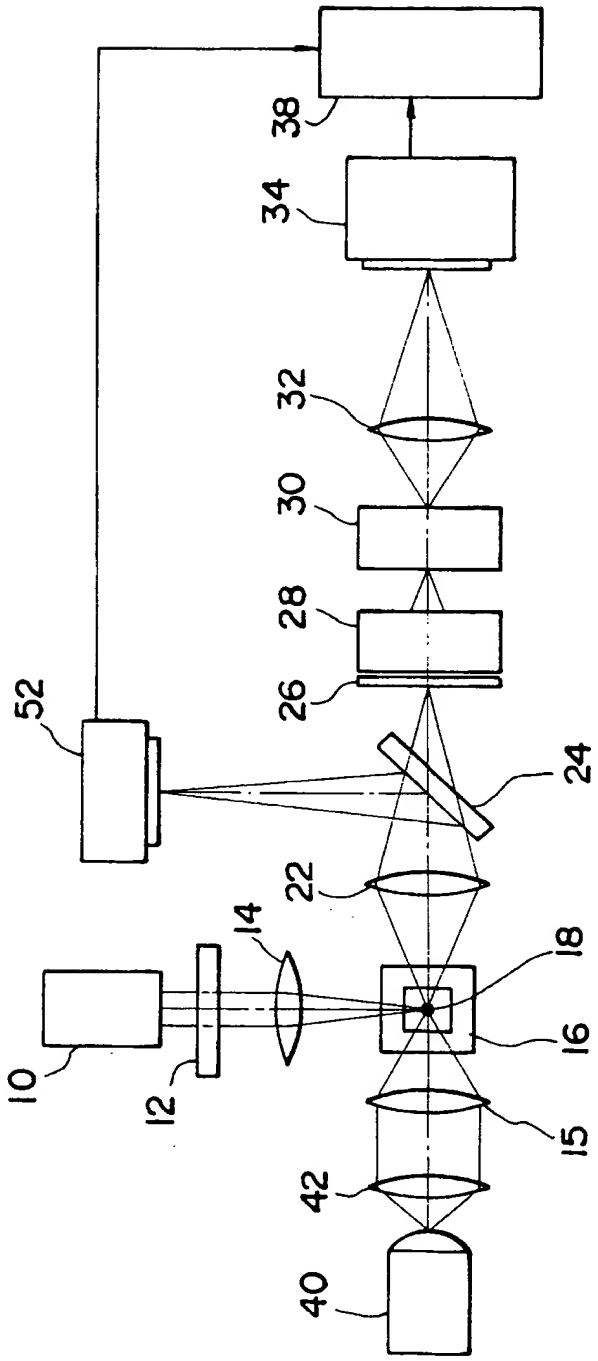


FIG.9

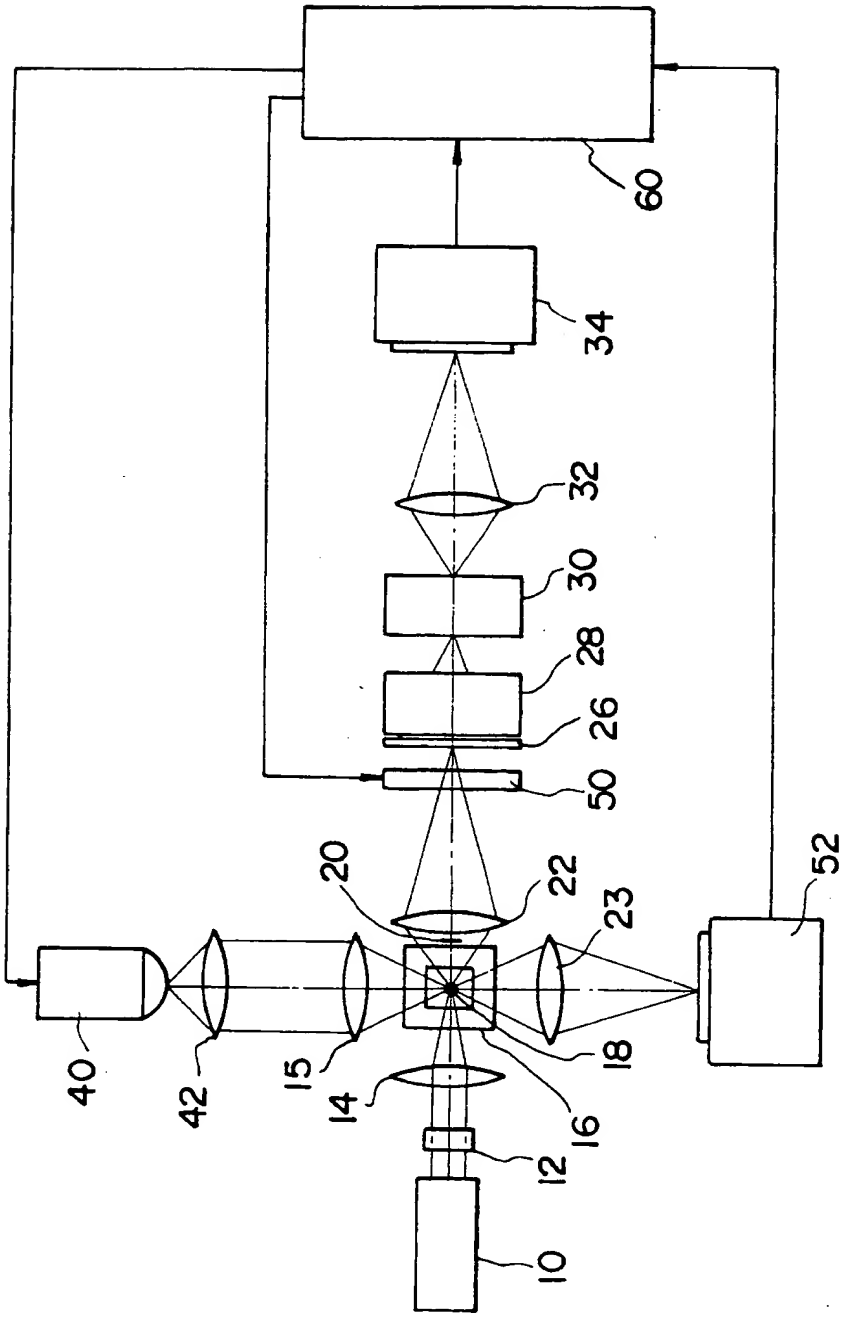


FIG.10

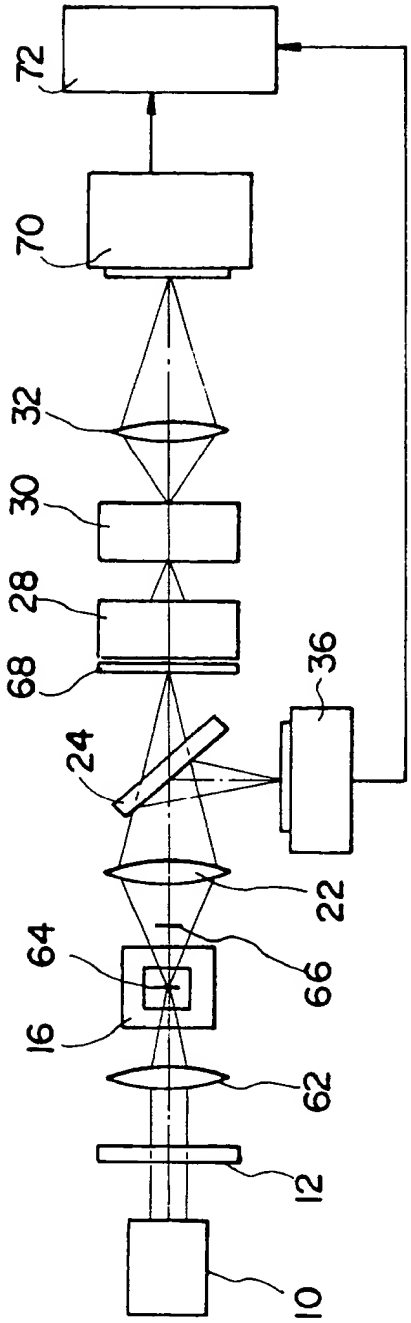
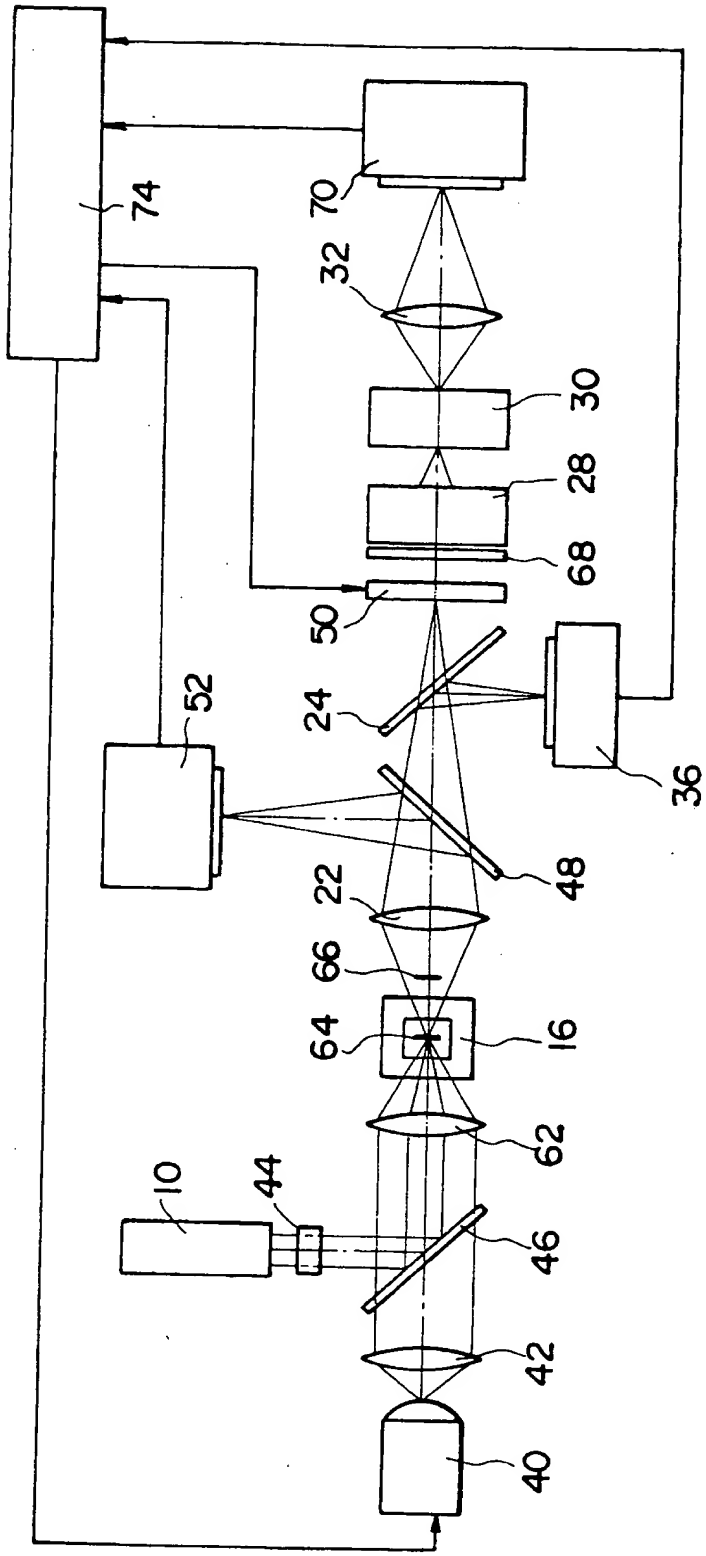


FIG.12



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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y	PATENT ABSTRACTS OF JAPAN vol. 13, no. 35 (P-818)26 January 1989 & JP-A-63 233 353 (SEIKO) 29 September 1988 * abstract * ---	1,10	G01N15/14
Y	US-A-4 793 705 (SHERA) * abstract * * column 3, line 12 - line 28 * * column 4, line 63 - line 64; figure 1 * ---	1,10	
D,A	PATENT ABSTRACTS OF JAPAN vol. 14, no. 169 (P-1032)30 March 1990 & JP-A-02 024 535 (CANON) 26 January 1990 * abstract * ---	1	
A	PATENT ABSTRACTS OF JAPAN vol. 16, no. 264 (P-1370)15 June 1992 & JP-A-04 065 654 (HITACHI) 2 March 1992 * abstract * ---	1,2,11	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
A	PATENT ABSTRACTS OF JAPAN vol. 16, no. 53 (P-1309)10 February 1992 & JP-A-03 252 542 (HITACHI) 11 November 1991 * abstract * ---	1,10	G01N
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A	EP-A-0 466 168 (TOA) * abstract; figure 1 * ---	1,6	
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	02 JULY 1993	THOMAS R.M.

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 442 025 (TOA) * abstract * * column 8, line 55 - column 9, line 7 * * figure 9 * -----	1,2,4,5	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	02 JULY 1993	THOMAS R.M.

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